

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>A61F 2/28</b>	<b>A1</b>	(11) International Publication Number: <b>WO 97/25941</b> (43) International Publication Date: <b>24 July 1997 (24.07.97)</b>
--	-----------	--

(21) International Application Number: **PCT/US97/00644**  
(22) International Filing Date: **16 January 1997 (16.01.97)**  
(30) Priority Data: **60/010,127** **17 January 1996 (17.01.96)** **US**

(71) Applicant (for all designated States except US): **OSTEOTECH, INC. [US/US]; 51 James Way, Eatontown, NJ 07724 (US).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DOWD, Michael [US/US]; 998 Kensington Drive, Eastampton, NJ 08060 (US). SCARBOROUGH, Nelson [US/US]; 47 Lambert Johnson Drive, Wayside, NJ 07712 (US). DAUGHERTY, Mark [US/US]; 2122 Sawmill Lane, Allenwood, NJ 08720 (US). McMICKLE, Jack [US/US]; 4550 Meadow Drive, Nazareth, PA 18064 (US).**

(74) Agents: **DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).**

(81) Designated States: **AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).**

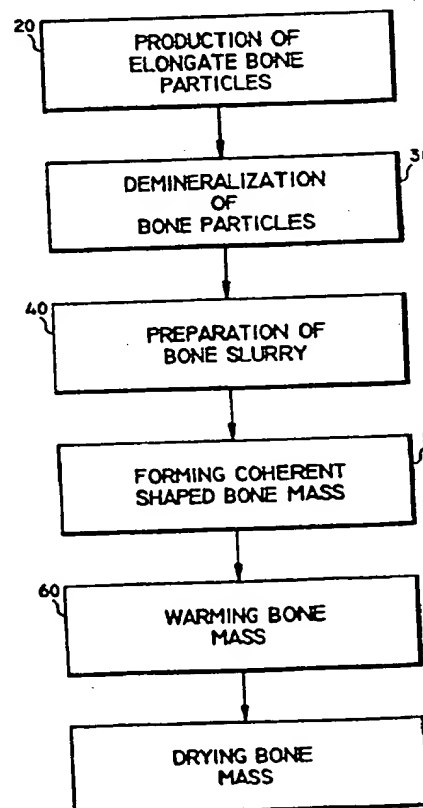
Published

*With international search report.*

(54) Title: **PROCESS AND APPARATUS FOR PRODUCING FLEXIBLE SHEETS FROM DEMINERALIZED, ELONGATE, BONE PARTICLES**

(57) Abstract

A process for fabricating shaped material from demineralized bone particles includes the steps of applying a liquid slurry of demineralized bone particles to a support, removing excess liquid from the demineralized bone particles to provide a coherent shaped mass of demineralized bone particles (50), and warming the shaped mass of demineralized bone particles at a predetermined temperature and for a predetermined time period (60). The resultant bone mass exhibits enhanced tensile strength and minimal bone particle disassociation upon rehydration thereby improving product handling and application at the operative site.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**PROCESS AND APPARATUS FOR PRODUCING  
FLEXIBLE SHEETS FROM DEMINERALIZED,  
ELONGATE, BONE PARTICLES**

**REFERENCE TO PROVISIONAL APPLICATION**

This application claims priority to U.S. provisional application No. 60/010,127, filed January 17, 1996.

**BACKGROUND OF THE INVENTION**

**1. Field of the Invention**

The present invention relates generally to surgically implanted materials fabricated from demineralized bone particles, and, more particularly, to such materials which are made up of a coherent shaped mass of elongate bone particles having an improved capacity to maintain its cohesive properties and exhibiting minimal bone particle disassociation upon rehydration.

**2. Description of Related Art**

The use of demineralized bone powder in the repair of bone defects has been a subject of investigation for some time. Bone powder contains one or more substances, possibly bone morphogenic protein (BMP), which induce bone regeneration at the defect site. See, e.g., Covey et al., "Clinical Induction of Bone Repair with Demineralized Bone Matrix or a Bone Morphogenetic Protein", Orthopaedic Review, Vol. XVII, No. 8, pp. 857-863 (August, 1989). According to Habal et al., "Autologous Corticocancellous Bone Paste for Long Bone Discontinuity Defects: An Experimental Approach", Annals of Plastic Surgery, Vol. 15, No. 2, pp. 138-142 (Aug. 1985), autogenous bone which has been granulated into a pastelike material and combined with autogenous blood has been used in the repair of long bone defects in dogs.

U.S. Patent No. 5,073,373 discloses a deformable, shape-sustaining osteogenic composition, suitable as a filler for osseous defects, in which particles of demineralized bone are uniformly distributed within a carrier which is a liquid polyhydroxy compound such as glycerol. The vast majority of the demineralized bone particles possess random, irregular geometries with an average median length to median thickness ratio of from about 1:1 to about 3:1.

Commonly assigned U.S. Patent No. 5,314,476 discloses a flowable osteogenic composition containing entangled demineralized bone particles of relatively high median length to median thickness ratio. The flowable osteogenic composition can possess a paste-like or putty-like consistency as well as a liquid or runny consistency.

Commonly assigned U.S. Patent No. 5,507,813 to Dowd et al., the contents of which are incorporated herein by reference, discloses a surgically implantable shaped material fabricated from elongate bone particles. The shaped material, e.g., in the form of a sheet, is formed by applying a liquid slurry of elongate bone particles, e.g., filaments or fibers, to a porous support, draining excess liquid from the bone particles, optionally while applying a compressive force to the particles during and/or after drainage of the excess liquid, to provide a coherent, shaped wetted mass of bone particles and, optionally, drying the wetted mass. The material thus formed is relatively rigid when dry and, upon contact with a biocompatible liquid, e.g., water, saline solution, etc., becomes pliable and flexible.

Although the shaped bone implant disclosed in the Dowd et al. '813 patent has proven to be quite effective in the repair of bone defects, the present invention is directed to further improvements in the process of fabricating such implants.

### **SUMMARY OF THE INVENTION**

Generally, the coherent shaped mass of demineralized bone particles produced in accordance with the principles of the present invention exhibit an enhanced capacity to retain its cohesive properties and experience minimal bone particle disassociation upon rehydration, thereby improving product handling and application at the operative site.

In a preferred embodiment, a process for fabricating shaped material from bone particles includes the steps of applying a liquid slurry of bone particles to a support, removing excess liquid from the bone particles to provide a coherent shaped mass of bone particles, and warming the shaped-mass of bone particles at a predetermined temperature and for a predetermined time period. Preferably, the bone particles are demineralized. The process may further include the step of drying, e.g., through lyophilization, the shaped-mass of demineralized bone particles subsequent to the step of warming. Preferably, a sheet of demineralized bone particles is produced.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

Preferred embodiments of the disclosure are described herein with reference to the drawings wherein:

FIG. 1 is a flow diagram illustrating the preferred process for fabricating shaped material from demineralized bone particles in accordance with the principles of the present invention;

FIG. 2 is a perspective view of an apparatus utilized to shape the demineralized bone particles into a sheet-like configuration;

FIG. 3 is a side-sectional view of the apparatus of FIG. 2;

FIG. 4 is a perspective view of a sheet mold utilized to hold the sheet of demineralized bone particles during the warming process;

FIG. 5 is a side-sectional view of the sheet mold of FIG. 4; and  
FIG. 6 is a side-sectional view of the sheet mold with a  
polypropylene lid.

### **DESCRIPTION OF THE PREFERRED EMBODIMENTS**

5                   Application of the shaped material of the present invention to the site  
of a bone defect, e.g., one resulting from injury, infection, malignancy or  
developmental malformation, leads to new bone ingrowth by one or more  
biological mechanisms such as osteogenesis, osteoconduction and/or osteoinduction  
or by one or more physical mechanisms such as constituting a physical barrier to  
10                   soft tissue ingrowth, providing a support or scaffolding for new bone growth, etc.

                  The term "osteogenic" as applied to the material of this invention  
shall therefore be understood as referring to the ability of the material of this  
invention to participate in the process of new bone growth regardless of the  
mechanism(s) involved.

15                   The term "coherent" as applied to the mass of elongate bone  
particles refers to the ability of the bone particles to adhere to each other either  
mechanically, e.g., by entanglement, or by use of a biocompatible adhesive  
whether the shaped material containing the bone particles is in the dry or wetted,  
e.g., hydrated, state.

20                   The term "shaped" as applied to the bone material of this invention  
shall be understood as referring to a determined or regular form or configuration,  
in contrast to an indeterminate or vague form or configuration (as in the case of a  
"lump" or other solid mass of no special form) and is characteristic of such  
materials as sheets, plates, disks, cones, pins, screws, and the like.

The term "rigid" shall be understood to refer to the relatively stiff, inflexible and somewhat brittle nature of the shaped materials of this invention while in the dry, i.e., unwetted, state.

The term "flexible" shall be understood to refer to the ability of the shaped material to become pliable upon being wetted or hydrated with a suitable biocompatible liquid and thus more readily conformable to a bone repair site.

Referring now to FIG. 1, a flow chart of the process for forming a shaped material from demineralized bone particles in accordance with a preferred embodiment of the present invention is illustrated. The process generally entails six (6) steps to form the desired shaped bone mass which, in the preferred embodiment, is a sheet of demineralized bone particles.

#### **Production of Elongate Bone Particles**

The first step of the process is the production of bone particles 20. Such particles can be readily obtained by any one of several methods, e.g., by milling or shaving the surface of an entire bone or relatively large section of bone. Employing a milling technique, particles ranging in median length from about 2 up to about 200 mm or more (as in the case of the long bones), in median thickness from about 0.05 to about 2mm and in median width from about 1 to about 20mm can be readily obtained. Another procedure for obtaining the elongate bone particles herein, particularly useful for pieces of bone of up to about 100 mm in length, is the Cortical Bone Shredding Mill available from Os Processing Inc., 3303 Carnegie Avenue, Cleveland, Ohio 44115. Use of this bone mill results in the production of long, thin strips which quickly curl lengthwise to provide tubular-like bone particles. Another apparatus and procedure utilized for obtaining bone particles is disclosed in commonly assigned U.S. Patent Appln. Serial No. 08/560,213, filed November 21, 1995.



Depending on the procedure employed for producing the elongate bone particles, one can obtain a mass of bone particles containing a specific weight percent, a median length and a median thickness. The aforementioned Dowd '813 patent discloses the use of bone particles containing at least about 60 weight percent, preferably at least about 70 weight percent and most preferably at least about 80 weight percent of bone particles possessing a median length of from about 2 to about 200 mm or more and preferably from about 10 to about 100 mm, a median thickness of from about 0.05 to about 2 mm and preferably from about 0.2 to about 1 mm and a median width of from about 1 mm to about 20 mm and preferably from about 2 to about 5 mm. These bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more and preferably from about 50:1 to about 100:1 and a median length to median width ratio of from about 10:1 to about 200:1 and preferably from about 50:1 to about 100:1.

If desired, the mass of elongate bone particles can be graded into different sizes to reduce or eliminate any less desirable size(s) of particles which may be present. In overall appearance, the elongate bone particles can be described as filaments, fibers, threads, slender or narrow strips, etc. As already noted and depending on the manner in which they are produced, these elongate particles may have a tendency to curl to provide tubular-like particles. The bone particles can be obtained from cortical, cancellous and/or corticocancellous bone which may be of autogenous, allogenic and/or xenogeneic origin.

### **Demineralization**

With reference again to the flow chart of FIG. 1, following the shaving, milling or other technique, the elongate bone particles are subjected to a demineralization process 30 to reduce their inorganic content to a low level, e.g.,

to not more than about 5% by weight of residual calcium and preferably to not more than about 0.5% by weight residual calcium. Demineralization of the bone particles will ordinarily result in producing particles of slightly smaller dimensions.

5 The elongate bone particles can be demineralized in accordance with known and conventional procedures. In a preferred demineralization procedure, the elongate bone particles are subjected to a defatting/ disinfecting step which is followed by an acid demineralization step. A preferred defatting/disinfectant solution is an aqueous solution of ethanol, the ethanol being a good solvent for lipids and the water being a good hydrophilic carrier to enable the solution to  
10 penetrate more deeply into the bone particles. The aqueous ethanol solution also disinfects the bone by killing vegetative microorganisms and viruses. Ordinarily at least about 10 to about 40 weight percent by weight of water (i.e., about 60 to about 90 weight percent of defatting agent such as alcohol) should be present in the defatting/disinfecting solution to produce optimal lipid removal and disinfection  
15 within the shortest period of time. The preferred concentration range of the defatting solution is from about 60 to about 85 weight percent alcohol and most preferably about 70 weight percent alcohol. Following defatting, the bone particles are immersed in acid over time to effect their demineralization. Acids which can be employed in this step include inorganic acids such as hydrochloric acid and organic acids such as peracetic acid. After acid treatment, the  
20 demineralized bone particles are rinsed with sterile water for injection to remove residual amounts of acid and thereby raise the pH. At this point some entanglement of the wet demineralized bone particles will result. The wet demineralized bone particles can then be immediately shaped into a shaped  
25 osteogenic material in accordance with the method of this invention or stored under aseptic conditions, advantageously in a lyophilized state, for processing at a later time.

The elongate bone particles can be admixed with one or more substances such as adhesives, fillers, plasticizers, flexibilizing agents, biostatic/biocidal agents, surface active agents, binding and bonding agents, fillers, and the like, prior to, during, or after shaping the particles into a desired configuration. Suitable adhesives, binding agents and bonding agents include acrylic resins, cellulose, bioresorbable polymers such as polyglycolide, polylactide, glycolide-lactide copolymer, etc. Suitable fillers include bone powder, demineralized bone powder, hydroxyapatite, etc. Suitable plasticizers and flexibilizing agents include liquid polyhydroxy compounds such as glycerol, monacetin, diacetin, etc. Suitable biostatic/biocidal agents include antibiotics, povidone, sugars, etc. Suitable surface active agents include the biocompatible nonionic, cationic, anionic and amphoteric surfactants.

If desired, the bone particles can be modified in one or more ways, e.g., their protein content can be augmented or modified as described in U.S. Patent Nos. 4,743,259 and 4,902,296. Any of a variety of medically and/or surgically useful substances can be incorporated in, or associated with, the bone particles either before, during or after fabrication of the shaped articles disclosed herein. Thus, e.g., one or more of such substances can be introduced into the demineralized bone particles, e.g., by soaking or immersing the bone particles in a solution or dispersion of the desired substance(s).

Medically/surgically useful substances which can be readily combined with the demineralized bone particles and/or osteogenic material of this invention include, e.g., collagen, insoluble collagen derivatives, etc., and soluble solids and/or liquids dissolved therein, e.g., antivirals, particularly those effective against HIV and hepatitis; antimicrobials and/or antibiotics such as erythromycin, bacitracin, neomycin, penicillin, polymyxin B, tetracyclines, viomycin, chloromycetin and streptomycins, cefazolin, ampicillin, azactam,

5 tobramycin, clindamycin and gentamicin, etc.; biocidal/biostatic sugars such as dextroal, glucose, etc.; amino acids, peptides, vitamins, inorganic elements, co-factors for protein synthesis; hormones; endocrine tissue or tissue fragments; synthesizers; enzymes such as collagenase, peptidases, oxidases, etc.; polymer cell  
10 scaffolds with parenchymal cells; angiogenic drugs and polymeric carriers containing such drugs; collagen lattices; antigenic agents; cytoskeletal agents; cartilage fragments, living cells such as chondrocytes, bone marrow cells, mesenchymal stem cells, natural extracts, tissue transplants, bone, demineralized bone powder, autogenous tissues such blood, serum, soft tissue, bone marrow,  
15 etc.; bioadhesives, bone morphogenic proteins (BMPs), transforming growth factor (TGF-beta), insulin-like growth factor (IGF-1); growth hormones such as somatotropin; bone digestors; antitumor agents; immuno-suppressants; permeation enhancers, e.g., fatty acid esters such as laureate, myristate and stearate monoesters of polyethylene glycol, enamine derivatives, alpha-keto aldehydes, etc.;  
and, nucleic acids. The amounts of such optionally added substances can vary widely with optimum levels being readily determined in a specific case by routine experimentation.

#### Preparation of Bone Slurry

20 With reference still to FIG. 1, subsequent to demineralization the next step 40 in the process involves the formation of the bone slurry from the demineralized product. Preferably, the bone particles are slurried in a suitable liquid, e.g., water, glycerol, organic protic solvent, aqueous solution, such as physiological saline, etc., and optionally containing one or more biocompatible ingredients such as adhesives, fillers, plasticizers, fertilizing agents,  
25 biostatic/bioaidal agents, surface active agents, medically/surgically useful substances, etc..., and allowed to reach equilibrium.

### Forming Coherent Shaped Bone Mass

The bone slurry is then subjected to a shaping step or process 50 to establish the coherent shaped bone mass. In the preferred embodiment, the bone mass is shaped into a flat-sheet like configuration; although, as stated above, other shapes including disks, cones, pins, screws, etc. are contemplated as well. An apparatus for forming the bone slurry into the sheet-configuration is depicted in FIGS. 2 and 3. This apparatus 100 includes a stand 102 having a basin 104 supported by a plurality of upstanding legs. A drain tube 106 extends from the lower surface of basin 102 and has an in-line valve 108. In-line valve 108 may be any conventional valve utilized to interrupt flow through tube 106 such as ball valves, gate valves, etc. A perforated stainless steel screen 110 is supported on the upper surface of stand 102. The screen 110 is replaceable.

The apparatus further includes a form tube 112 which is mounted by hinge 114 to stand 102. Form tube 112 pivots about hinge 114 between the open position depicted in FIG. 2 and the closed position depicted in FIG. 3. Form tube 112 has a peripheral flange 116 which is dimensioned to sit above the border of the screen 110 supported on the upper surface of stand 102. In the closed position of form tube 112, the peripheral flange 116 is compressed against the top surface of stand 102, sealingly securing the border of perforated screen 108 therebetween. As shown, stand 102 may have a peripheral elastomeric seal 118 to enhance sealing engagement of form tube 112 and the stand 102. A latch assembly 120 may be provided to releasably secure form tube 112 in the closed position. Any conventional latch assembly may be utilized. Form tubes having various shapes or dimensions may be employed with the apparatus.

To continue the process, the liquid slurry containing the demineralized elongated bone particles is poured into form tube 112. At such time, in-line valve 108 is in a closed condition to prevent discharge from the

apparatus. Valve 108 is opened, and the liquid from the slurry drains through perforated screen 110, leaving a wetted layer of bone particles on the screen. This procedure is referred to herein as "wet-laying". It is to be noted that the bone particles are advantageously uniformly deposited on perforated screen 110 thereby forming a layer of bone material having a constant or uniform thickness. Thereafter, latch assembly 118 mounted to form tube 112 is opened and perforated screen 110 is then removed.

The layer of wetted bone particles removed from apparatus 100 is blotted dry using an absorbent material. A compressive force or weight may be applied to the absorbent material to facilitate drying of the bone particles. A sheet of Tyvek may be placed on top of the layer of bone particles for support and the screen is turned over and removed to expose the other surface of the wetted bone particles. This side is then blotted dry in the manner discussed above and a sheet of Tyvek is placed on the surface. At such a time, the bone sheet is sandwiched between two Tyvek sheets.

The result of the wet-laying procedure with apparatus 100 is the shaping of the demineralized bone particles to provide a coherent sheet of bone particles. The thickness of the layer of wetted bone particles can vary widely and is dependent upon the amount of bone slurry deposited into the form tube. Either before or after the wet-laying procedure, one or more additional substances can be added to the bone particles, e.g., thixotropic agents, therapeutic agents, and the like as previously mentioned.

#### Warming of Bone Sheet

Subsequent to forming of the bone sheet, the bone sheet is prepared for warming 60. With reference to FIGS. 4 and 5, the formed bone sheet (with or without the Tyvek sheets) is preferably positioned within a sheet mold 300. Sheet

mold 300 includes a perforated polypropylene base 302 and solid metallic lid 304 which is mountable to the base 302. In FIG. 4, solid lid 304 is shown disassembled from base 302 and inverted. Solid lid 304 includes inner raised portion 306 which is accommodated within an inner-recess 308 of base 302 when in the assembled condition whereby peripheral ledge 310 of the lid 304 rests on shelf 312 of the base 302. Metallic lid 304 is made from stainless steel, although, any conductive metallic material could be used as well.

As best depicted in FIG. 5, solid lid 304 when mounted to base 302 defines a gap or clearance "c" between the surfaces of the lid 306 and the base 302. The gap or clearance preferably approximates the thickness of the bone sheet which is to be positioned therein.

In accordance with the heating step, the bone sheet is initially placed into base 302 and the metallic lid 304 is secured thereto with the use of latches 312. Latches 312 may be any conventional latch suitable for this purpose. It is to be appreciated that solid lid 104 exerts a slight compressive force on the bone sheet thereby ensuring a constant thickness of the bone sheets over multiple uses. The mold 300 with bone sheet is then placed into a heating chamber such as an oven, a lyophilizer (with no vacuum applied) or a warming plate and the bone sheet is warmed for a predetermined time at a controlled temperature. In a preferred embodiment, the bone sheet is warmed for a period ranging from about 2 hrs. to about 4 hrs., more preferably, 3 hrs., at a temperature ranging from about 25° to about 55°C, most preferably, about 45°C. During warming some moisture evaporates from the bone sheet through the perforations of base 302. Compression of the bone sheet by lid 304 facilitates this evaporation and/or drainage as well.

In the preferred embodiment, the bone sheet is at least partially warmed through conductive heat transfer by the metallic plate. It is envisioned that the bone sheet may be heated without the use of the mold through direct

heating methods or alternatively the metallic lid may be subjected to heat energy whereby the bone sheet is heated solely through conductive transfer through the lid. Alternate sources of heat energy include microwave, radio-frequency, laser, etc.

5

The warmed bone sheet is thereafter removed from the heating device. Upon its removal, the sheet is in a flexible and pliable condition. It is to be appreciated that the heating step advantageously improves the capacity of the bone sheet to maintain its cohesive properties and, in addition, it minimizes bone particle disassociation thereof, particularly, upon rehydration.

10

#### Drying of Bone Sheet

15

The wet demineralized bone particles may then be optionally subjected to drying step 70, preferably by lyophilization in accordance with procedures and conditions that are well known in the art, e.g., a shelf temperature of from about -20 to about -60°C, a vacuum of from about 150 to about 100 mTorr for a time of from about 4 to about 48 hours depending on the bone mass. With reference to FIG. 6, metallic lid 304 is removed from base 302 and a polypropylene lid 320 is mounted to the base 302. Polypropylene lid 320 is identical in configuration to metallic lid but includes perforations 322 to permit escape of moisture therethrough during lyophilization. Once polypropylene lid 322 is mounted to base 302 and latched shut through latches 312, the mold 300 is placed in the lyophilizer apparatus. Upon completion of the lyophilization, polypropylene lid 320 is removed permitting the removal of the bone sheet. The resulting shaped sheet is rigid and relatively strong when dry and flexible and pliable when wetted or hydrated.

20



At the site of implantation, the shaped article can be employed in the dry state or, where site conformation is desired, in the hydrated state. The dry or hydrated article can be cut or sized if need be to conform to a site being repaired. The article can be hydrated with a suitable biocompatible liquid, e.g., water, saline solution, etc., for a period of time ranging from about 1 to about 120 minutes depending on the density of the shaped material. After being hydrated, the shaped material becomes flexible yet retains its shape and much of its strength. The shaped material of this invention can be packaged in either the dried or wet state and stored for subsequent application. In some circumstances, it is preferable to package the material in the wet state so that it is ready for immediate use at the surgical site.

The shaped materials of this invention can be utilized in a wide variety of orthopaedic, neurosurgical and oral and maxillofacial surgical procedures such as the repair of simple and compound fractures and non-unions, external and internal fixations, joint reconstructions such as arthrodesis, general arthroplasty, cup arthroplasty of the hip, femoral and humeral head replacement, femoral head surface replacement and total joint replacement, repairs of the vertebral column including spinal fusion and internal fixation, tumor surgery, e.g. deficit filling, discectomy, laminectomy, excision of spinal cord tumors, anterior cervical and thoracic operations, repair of spinal injuries, scoliosis, lordosis and kyphosis treatments, intermaxillary fixation of fractures, mentoplasty, temporomandibular joint replacement, alveolar ridge augmentation and reconstruction, inlay bone grafts, implant placement and revision, sinus lifts, etc. These materials can be sutured or stapled in place for anchoring purposes and serve in guided tissue regeneration or as barrier materials.

The bone sheet produced in accordance with the process of the present invention (i.e., utilizing the warming step) exhibits enhanced capacity to maintain its cohesive properties and minimal bone particle disassociation upon rehydration. Consequently, product handling and application at the operative site is enhanced.

5

It will be understood that various modifications may be made to the embodiment disclosed herein. For example, various lengths and types of sutures may be employed. Therefore, the above description should not be construed as limiting but merely as an exemplification of a preferred embodiment. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

10

**WHAT IS CLAIMED IS:**

1. A process for fabricating shaped material from bone particles, comprising the steps of:  
applying a liquid slurry of bone particles to a support;  
5 removing excess liquid from the bone particles to provide a coherent shaped mass of bone particles; and  
warming the shaped-mass of bone particles at a predetermined temperature and for a predetermined time period.
2. The process according to claim 1 wherein the liquid slurry  
10 comprises demineralized bone particles.
3. The process according to claim 2 including the step of drying the shaped-mass of demineralized bone particles subsequent to the step of warming.
4. The process according to claim 3 wherein the step of drying  
15 includes subjecting the shaped-mass of demineralized bone particles to a lyophilization process.
5. The process according to claim 2 further including the step of compressing the shaped-mass of demineralized bone particles during the step of warming.
- 20 6. The process according to claim 2 wherein the step of applying includes pouring the liquid slurry of demineralized bone particles onto a porous support to provide a sheet of demineralized bone particles.

7. The process according to claim 6 further including the step of positioning the sheet of demineralized bone particles into a correspondingly dimensioned porous mold support.

5 8. The process according to claim 7 wherein the step of warming includes placing the mold support and the sheet of demineralized bone particles into a heating device.

10 9. The process according to claim 2 wherein the step of applying includes applying a liquid slurry of demineralized bone particles comprising cortical, cancellous and corticocancellous bone of autogenous, allogenic and xenogeneic origin.

10. The process according to claim 2 wherein the step of warming includes subjecting the shaped mass of demineralized bone particles to a temperature ranging from about 22°C to about 55°C for a period of time ranging from about 2 hours to about 4 hours.

15 11. The process according to claim 10 wherein the step of warming includes subjecting the shaped mass of demineralized bone particles to a temperature ranging from about 45°C for a period of time about 3 hours.

12. The shaped mass of demineralized bone particles produced in accordance with claim 1.

20 13. The shaped mass of demineralized bone particles produced in accordance with claim 2.

14. The shaped sheet of demineralized bone particles produced in accordance with claim 3.

15. The shaped sheet of demineralized bone particles produced in accordance with claim 6.

5 16. A process for forming a sheet of demineralized bone particles, comprising the steps of:  
applying a liquid slurry of demineralized bone particles to a porous planar support surface;  
draining excess liquid from the demineralized bone particles  
10 to provide a coherent sheet of demineralized bone particles;  
positioning the sheet of demineralized bone particles into a correspondingly dimensioned porous mold;  
subjecting the sheet of demineralized bone particles within the mold to heat at a predetermined temperature for a predetermined time period; and  
15 drying the sheet of demineralized bone particles.

17. The process according to claim 16 wherein the step of drying includes subjecting the sheet of demineralized bone particles to a lyophilization process.

20 18. The process according to claim 17 wherein the step of drying includes positioning the sheet of demineralized bone particles disposed in the mold within a lyophilization chamber.

19. The process according to claim 16 including the step of compressing the sheet of demineralized bone particles while subjecting the sheet to heat.

5 20. The process according to claim 19, the step of compressing includes placing a compressive cover on to the mold to apply compressive forces to the sheet of demineralized bone particles disposed therein.

21. A bone product comprising a coherent heat-treated shaped-mass of demineralized, elongated bone particles.

10 22. The bone product according to claim 21 wherein the coherent heat-treated shaped-mass of demineralized elongated bone particles has greater cohesive properties than a shaped-mass of demineralized elongated bone particles which has not been heat-treated.

1/6

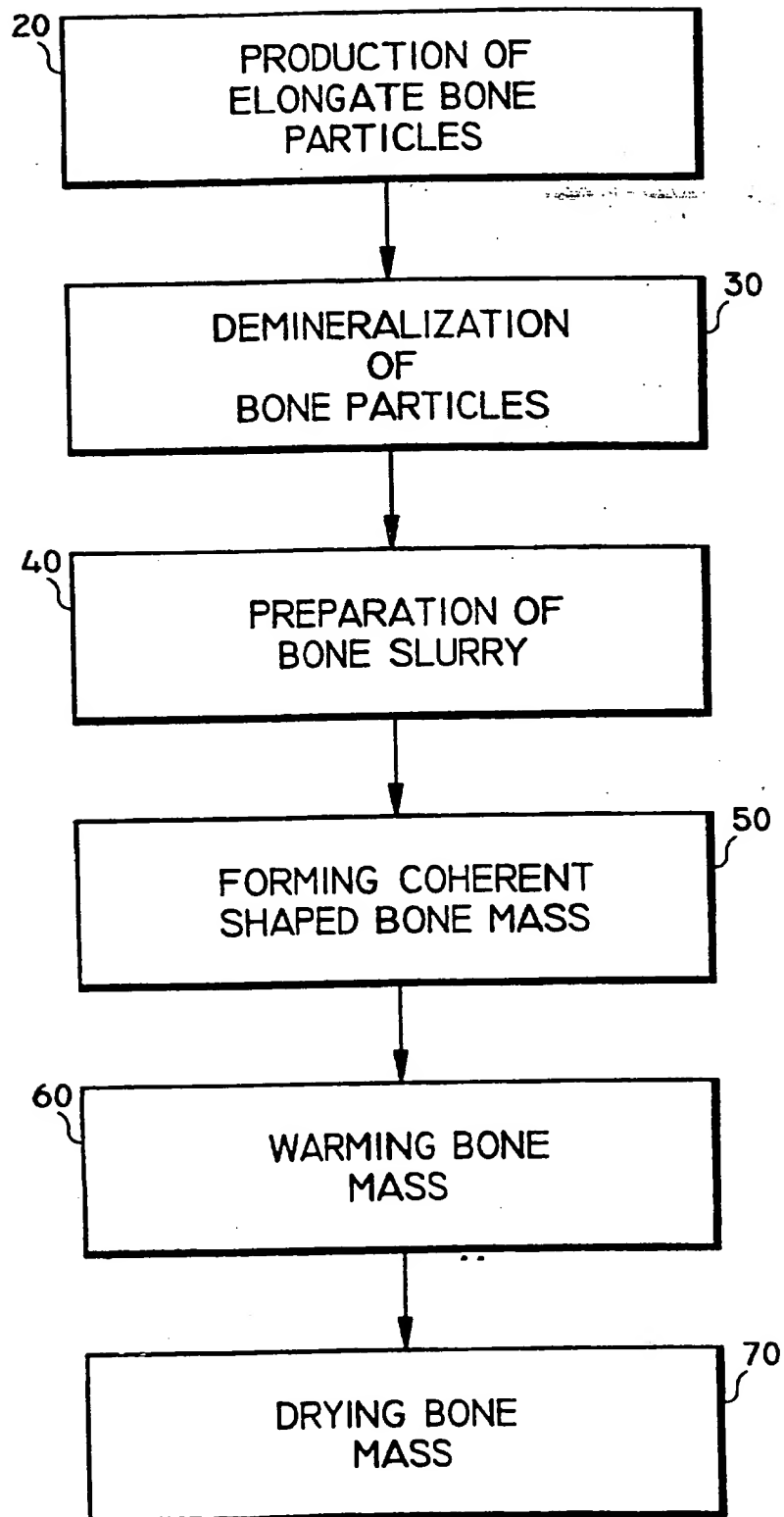


FIG. 1

SUBSTITUTE SHEET (RULE 26)

2/6

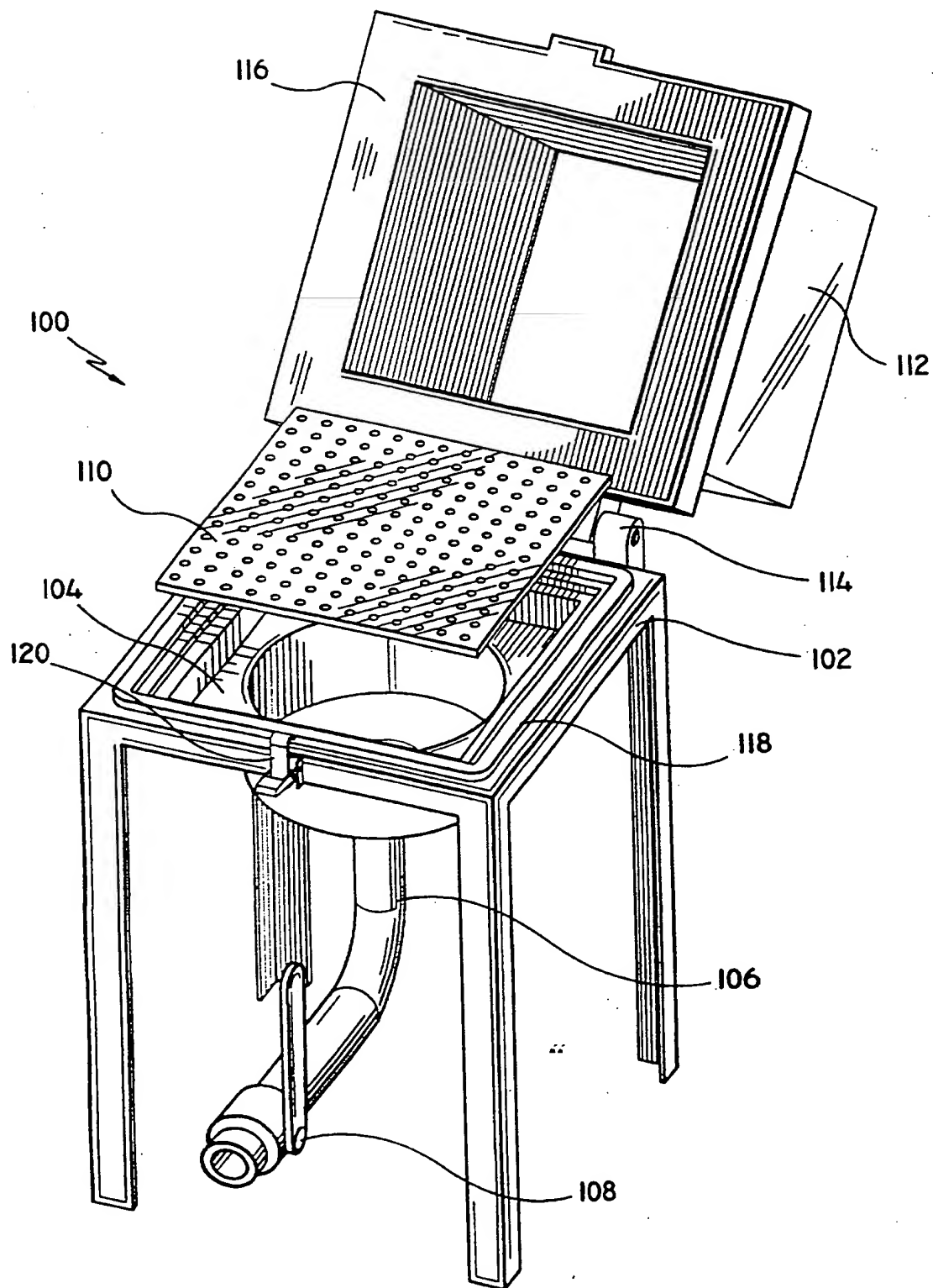


FIG. 2

SUBSTITUTE SHEET (RULE 26)



3/6

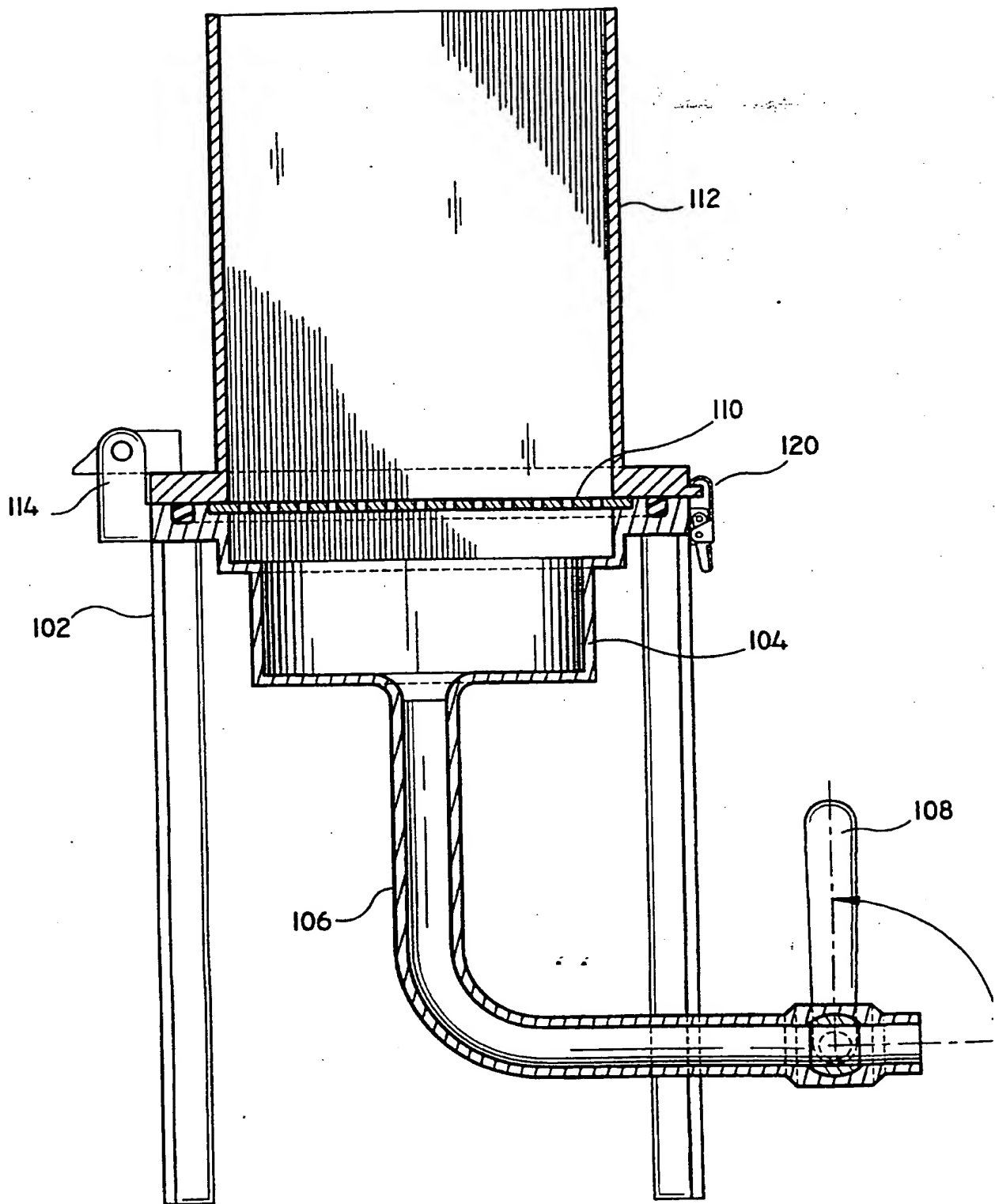


FIG. 3

SUBSTITUTE SHEET (RULE 26)

4/6

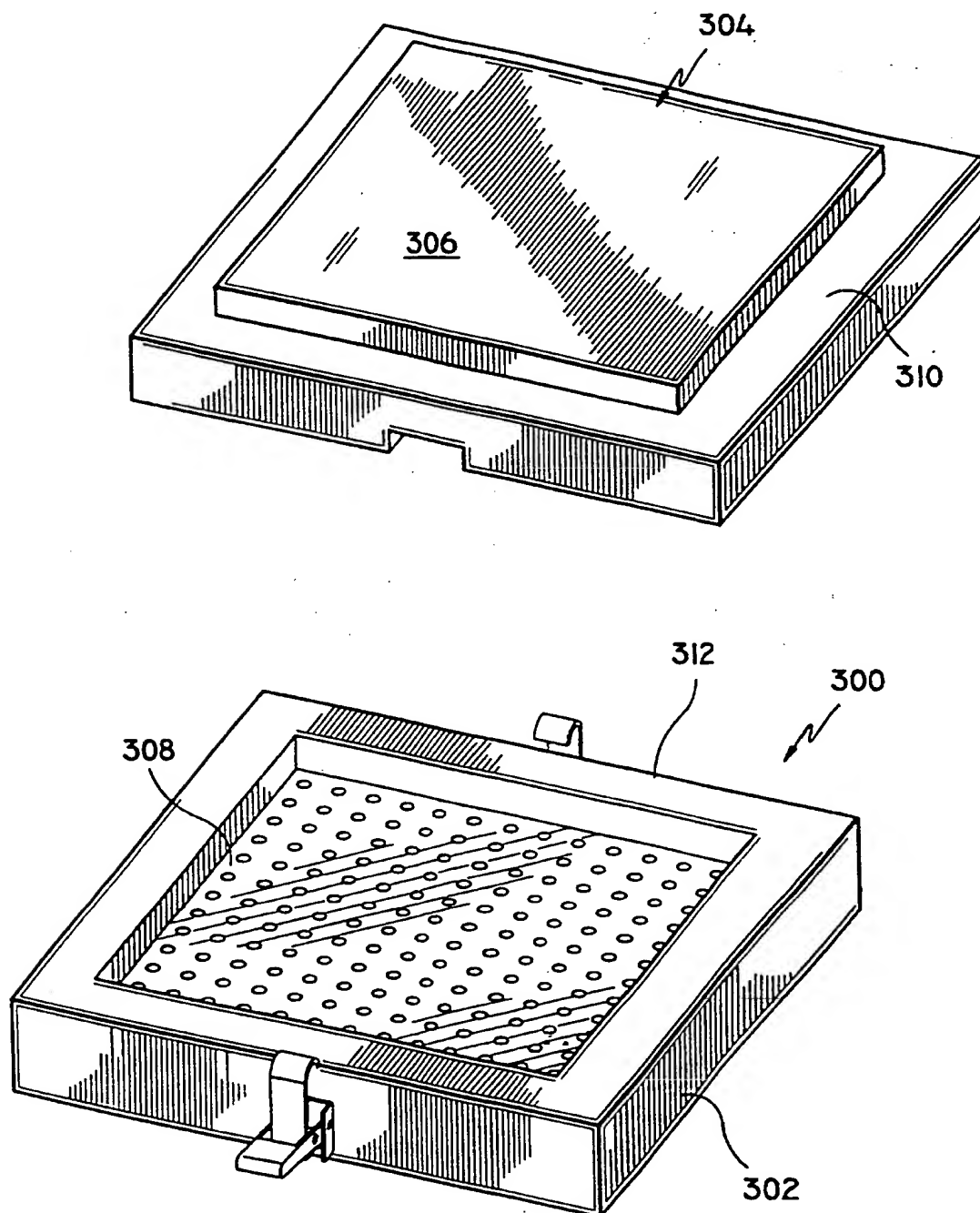


FIG. 4

SUBSTITUTE SHEET (RULE 26)

5/6

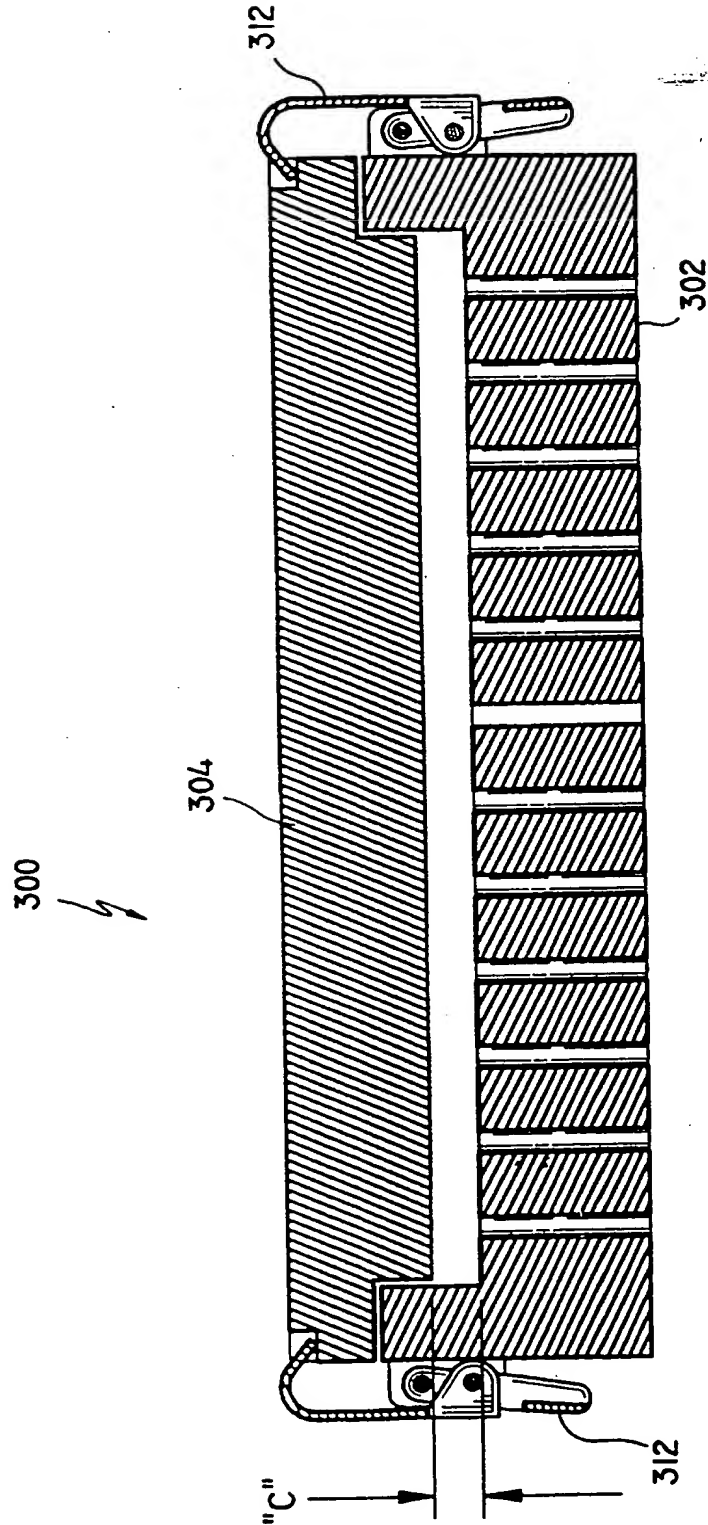


FIG. 5

SUBSTITUTE SHEET (RULE 26)

6/6

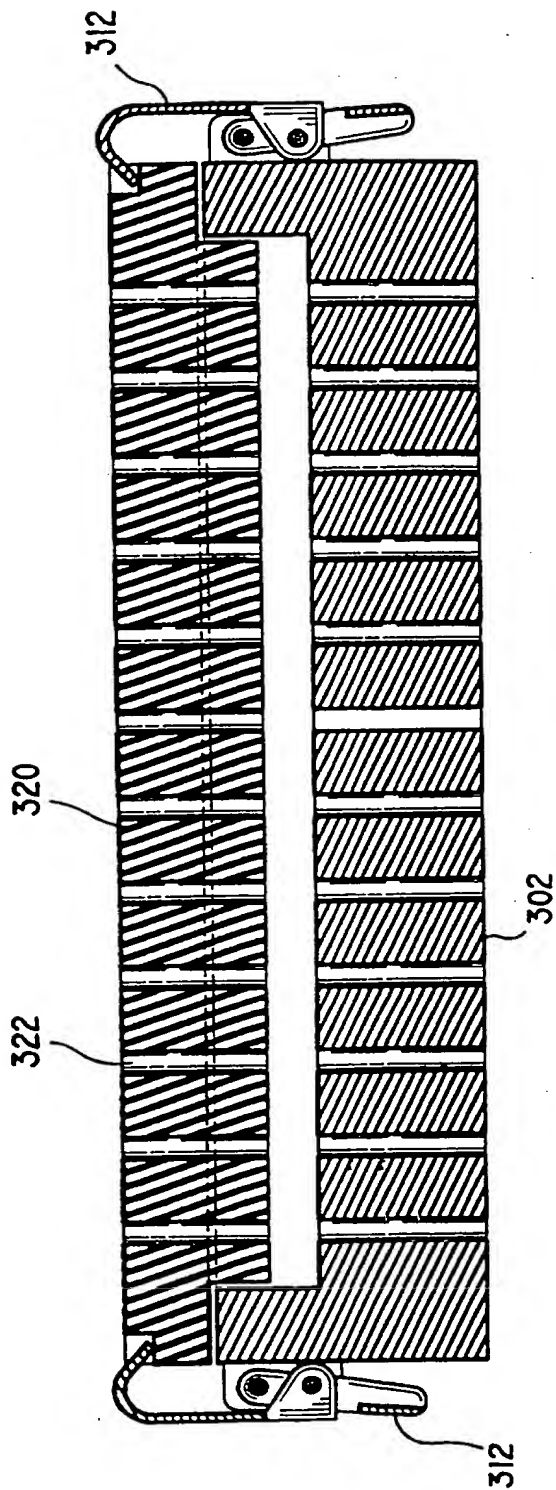


FIG. 6

300

SUBSTITUTE SHEET (RULE 26)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/00644

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 2/28  
US CL :623/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 623/11, 16, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

search terms: bone particle/(3a)demineralize/ or dbp and slurry and heating or heat or warming and shaped or shaping

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	US 5,507,813 A (DOWD et al) 16 April 1996, whole document.	1, 2, 5, 6, 9, 12, 15, 21, 22 ----- 3, 4, 7, 8, 10, 11, 14, 16-20
Y	US 5,123,925 A (SMESTAD et al) 23 June 1992, entire document.	1, 12
Y	US 5,314,476 A (PREWETT et al) 24 May 1994, entire document.	1, 12
Y	US 5,306,304 A (GENDLER) 26 April 1994, entire document.	1, 13, 14, 15, 21, 22.

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

A

document member of the same patent family

Date of the actual completion of the international search

14 MARCH 1997

Date of mailing of the international search report

08 APR 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3590

Authorized officer

PAUL PREBILIC

Telephone No. (703) 308-2905